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CO-TRANSPLANTATION OF HLA-MATCHED RELATED DONORS CULTURE-EXPANDED MESENCHYMAL STROMAL CELLS AND HEMATOPOIETIC STEM CELLS IN THALASSEMIA MAJOR PATIENTS

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Objective: Use of mesenchymal stromal cells (MSCs) in hematopoietic stem cell transplantation (HSCT), either for enhancement of hematopoietic engraftment or for prevention of graft versus host disease (GVHD) is currently unknown. Following a positive phase II study in all classes of thalassemia major, in this study we aimed to show that co-transplantation of MSC and hematopoietic stem cells (HSCs) from HLA-matched related donors after conditioning regimen is safe and could facilitate engraftment and decrease GVHD.
Methods: Between November 2006 and October 2009, 48 class III thalassemia major patients were enrolled. In this double-blind randomized clinical trial, HLA-identical related donors HSC were transplanted (non-MSCs group, n = 23 with median age of 16yrs and F/M = 11/12) or co-transplanted with MSCs (MSCs group, n = 25 with median age of 17yrs and F/M = 8/17) in thalassemia major patients. Patients received Cyclophosphamide-based or Fludarabine-based conditioning regimens and short course methotrexate and cyclosporine as GVHD prophylaxis. On day 0, MSCs group patients were given MSCs intravenously 4 hours before infusion of either bone marrow or peripheral blood stem cells. The number of MSCs infused was 1.45-1.80×10^6/kg.
Results: MSCs infusions were well tolerated. The median time to neutrophil engraftment (absolute neutrophil count >0.5×10^9/L) was 14 days for MSCs group and 13 days for non-MSCs group (p-value = 0.16). The median time to platelet engraftment (platelet count >20×10^9/L) was 16 and 15 days, respectively (p-value = 0.34). Acute GVHD grade III-IV was observed respectively, in 6(24%) and 4(17.5%). (p-value = 0.73). Median follow-up duration for alive patients was 10 months (ranged 1-28).
Conclusion: In this study we demonstrated that co-transplantation of HLA-matched related donors MSCs with HSCs is seems to be safe. We didn't find statistical significant difference in acute GVHD incidence, rate of non-engraftment, mortality rate and median time to neutrophil and platelet recovery between two groups. Most probably explanations are small number of patients in study groups and short follow-up period.

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STROMAL ELEMENTS AND ENGRAFTMENT IN AUTOLOGOUS HEMATOPOIETIC PROGENITOR CELL (HPC) TRANSPLANT FOR MYELOMA

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Introduction: Homing of HPC after transplant may be related to stromal elements of the hematopoetic stem cell niche. We present a retrospective analysis of bone marrow (BM) biopsies from patients with myeloma prior to autologous HPC transplant and correlate stromal variables with engraftment.
Material and Methods: 25 consecutive patients who underwent autologous HPC transplant and survived 100 days post-transplant were identified. BM biopsies done just prior to transplant were analyzed using hematoxylin and eosin stained sections to evaluate the following histological parameters: stromal components (fat, regenerating adipocytes, fat necrosis, stromal edema, vasculature and stromal hemorrhage); bone remodeling (osteoblasts vs osteoclasts); hematopoeisis (endosteal vs peri-sinusoidal hematopoesis); cellularity; and interstitial fibrosis. Disease specific parameters including duration of disease before transplant, conditioning therapy for transplant, and total viable CD34 stem cells infused for transplant were also identified. Time to platelet engraftment of 20,000/cmm and 50,000/cmm and time to WBC engraftment (ANC ≥500/cmm) were determined. Univariate and multivariate regression analysis were applied to determine, in a step-wise fashion, the correlation of independently significant BM stromal parameters with engraftment.
Results: The median time to platelet engraftment of 20,000/cmm and 50,000/cmm were 12 and 16 days respectively. The median time to WBC engraftment was 11 days. Sinusoidal hematopoesis was significantly correlated with delayed platelet engraftment to 20,000 (≥ 12 days) (p = 0.034). Stromal edema correlated with delayed WBC engraftment (≥ 11 days) (p = 0.042). No other variables examined were statistically significant.
Conclusion: Pretransplant BM biopsy evaluation for stromal injury as demonstrated by stromal edema and peri-sinusoidal hematopoiesis may be useful markers for predicting delayed platelet and WBC engraftment in patients undergoing HPC transplant for myeloma.

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MESENCHYMAL STEM CELLS: HEALTHY AT ANY AGE

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Mesenchymal Stem Cells (MSC) are gaining in popularity as an experimental therapy for a number of conditions including graft-versus-host disease, Crohn's disease, myocardial infarction, etc. Most applications require that MSCs be expanded to achieve an adequate cell-dose for therapy. Prior data suggest that MSC undergo aging in culture and that MSC from older donors undergo earlier senescence than MSC from younger donors. We have observed over 100 MSC expansion cultures and it seemed that early in the expansion period MSC from any age donor microscopically appeared healthy and showed no difference upon differentiation into adipogenic, osteogenic, or cartilage lineages. We hypothesized that MSC from any age donor would have similar cellular fitness when expanded under incubation conditions and limited passage to mimic cell handling that would be used in a clinical preparation. We have compared the expression of several markers of aging in MSCs obtained from a subset of 120 donors over a wide range of ages (8 months to 60 years). We find that although MSC from older individuals produced slightly fewer cells over a fixed number of passages and have a slightly longer doubling time (54 hrs vs 42 hrs), a satisfactory clinical product can still be obtained (multiple doses at >106 cell/kg). When MSC from young (0.8-6 years) and old (43-60 years) were compared there was no difference in cell surface markers, lipofuscin, migration ability, or expression of aging markers such as iNOS, PGE2, p16, and SOD. SOD activity (0.025 vs 0.028 U/ml) and oxidative challenge death rate to hydrogen peroxide were not significantly different (1% vs 1.5%, p = 0.14). Morphology by light microscopy and extent of qualitative differentiation into osteogenic, adipogenic, and cartilage cell types were also similar in old and young donor derived MSC. Finally, telomeres did not show a significant difference in length between young and old donor-derived MSC early in passage. We conclude that age may not need to be considered when determining a potential MSC donor especially in light of the fact that many clinical applications require only a limited culture time (19-21 days) to achieve a sufficient number of cells for a useful clinical product.

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AFRICAN AMERICAN ADULT DONORS RESPOND TO G-CSF WITH PROGENITOR CELL YIELDS COMPARABLE TO CAUCASIAN AND HISPANIC DONORS

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Background: Because African Americans (AAs) have lower leukocyte counts and cord bloods from AA neonates have fewer progenitor cells, we examined the responses to G-CSF and progenitor cell yields in healthy adult AAs.